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(54) Title of Invention Entero-Soluble Capsule

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(72) Inventor: Yoshioka, Toshimitsu

Chie Building Fujimi 304

30-38 4-chome Fujimi Sayama-shi Saitama-ken

(72) Inventor: Kimura, Toshiaki

47-20 4-chome Sayamadai Sayama-shi Saitma-ken

(71) Applicant: Snow Brand Milk Products Co., Ltd. 6-1-1-Naebocho, Higashiku, Sapporo, Hokkaido

(74) Representative Patent Attorney Funahashi, Eiko

ENTERO-SOLUBLE CAPSULE

Industrial Field of the Invention

This invention relates to entero-soluble capsules that are effectively dissolved within the intestine. More specifically, the invention relates to an entero-soluble capsule that when orally ingested has enteral effective substances or heat sensitive substances that start to disintegrate when reaching the intestine, but whose activity is not damaged by gastric fluid or acids within the gastric fluid.

Related Art

Conventionally, the effective substances have been proposed for within the intestine, such as bifidobacteria, as one method, in order to protect from outside conditions such as acids that are sometimes coated with fat dissolvable at the body temperature (Kokai S57-33543) and as another method, solidify a mixture of bacteria and its protective membrane solution by injecting into a

saline solution which is used for congealing and after drying, as necessary, the solidified matter is coated with oil having a melting point at or above body temperature to obtain microorganisms with high preservability (Kokai S60-141281).

However, using the former method, because oil which shows fluidity at 35°C and above is used, for the bifidobacteria which is coated using this kind of oil, when orally ingested, the oil within the mouth or within the intestine disintegrated and because of this collapse, the problem arises that the bifidobacteria is almost completely killed by the gastric fluid before reaching the intestine. In addition, with only mixing the bifidobacteria and oil as a coating, this mixture cream is only ingested using limited methods.

In addition, the latter method's cost becomes high because the processes become complicated in order to coat with oil, after encapsulating the substances having bacteria, moisture control functions and dehydrating shock prevention functions using calcium alginate, so that the latter method is a problem.

At the same time, one entero-soluble capsule has its core substance as an entero-soluble substance within a wall membrane comprised of ethyl cellulose (Kokai S58-67616) and another capsule as a double formation by coating for a wall membrane substance using complex coacervate membrane comprised of polymer membrane such as polystyrene, polyputadiene, styrene methyl acrylate

copolymer, a gelatin on top, and an entero-soluble polymer electrolyte (Kokai S55-105615).

Problems that the Invention is to Solve

However, both methods are troublesome because of their complexity and there has yet to be reported methods that are simple. That is, there is technology which coats bifodobacteria or gel using oil in order to elevate the preservability of the bifodobacteria, but multi capsules which uniformly disperse in oil bifodobacteria granules as in this invention have not been obtained.

This invention has the goal of absorbing entero-soluble substances, such as bifodobacteria, within the intestine, and by encapsulating using granulaes medicinal substances showing activity without absorption within the intestine, the capsules are not destroyed in the mouth or intestine even when orally ingested, providing entero-soluble capsules which reach the intestine and begin to be dissolved easily.

Means for Solving the Problems

This invention is an entero-soluble capsule which disperses to hardened oils having melting points exceeding the body's temperature granules of enteral effective substances or heat sensitive substances and encapsulates them.

The enteral effective substances are ① medicinal substances which are exposed to physiological activity reduction by gastric fluid and the enzymes within the

gastric fluid, enzymes such as pancreatin, medicinal substances such as erythromycin or hormonal agents, ② substances which sometimes impart soluble stimulus to the intestine and substances whose use damages the elimination function, for example, Atebrin salicyclic acid and tannic acid, ③ medicinal substances densely used in the intestine, for example, anti parasite agents and antifungal agents within the intestine and ④ enteral effective substances which are easily eliminated by gastric acid, for example, bifodobacteria.

In addition, heat sensitive substances, in temperature regions from above the temperature of the human body to the boiling point of water, after remaining undisturbed for a period of time, experience changes in structure and colour from the effects of the heat as well as experience substance activity failures. These substances are called denaturalized substances. Vitamin C is one concrete example of heat sensitive substances as well as every kind of enzymes or useful bacteria.

When using bifidobacteria in encapsulating, the concentration of the bifidobacteria within the obtainable product, considering the required amount of daily ingestible amount and because 10^7-10^9 units/g are necessary per product, it is desirable to have highly concentrated cultured bacteria granules. The concentration level is 10^9-10^{11} units/g. Mixing these highly concentrated cultured bacteria granules with approximately 10 times by weight hardened oils and fats gives a hardened oil and fat capsule having 10^5-10^{10}

units/g. When the bifidobacteria consists of granules, there is no effect even when immersing in oil and fat at 40-60°C for a short time, say, 30 minutes or less and there is no change in the viable cell count.

By way of example for an adjustment method appropriate for entero capsules, there has been demonstrated encapsulating methods by drying methods within liquids, spray drying methods, and spray cooling methods, but among these, it is desirable to use the spray cooling methods because of its ① high encapsulating rate and ② the fine particle diameters.

For example, after dissolving the hardened oil and fat at a melting point of 45°C in a jacket system tank, bifidobacteria dried granules are rapidly dispersed in the oil. While stirring to make the dispersed liquid uniform, supply by nozzle a constant flow amount using a pump (snake pump, gear pump, and plunger pump) and spray within a chamber using cooling air as a parallel flow. In this case, the cooling air is not flowing in parallel, but even if the flow is a counter flow, there are no ill effects. Cooling occurs at a required and sufficient cooling temperature and solidifying period for the hardened oil to solidify. The cooling air temperature for cooling is -80 to 20°C. Under these conditions, it is possible to obtain a capsule of a diameter in the range of 30-2000μm. When considering solubility within the intestine, diameter ranges of 50-1000μm are desirable. The capsule that is obtained is a multiple capsule for

which the capsule substances are uniformly dispersed in the oil and fat.

It is desirable for the enteral effective substances or heat sensitive substances, which are multi-encapsulated using granules, to add granules such as powdered skim milk, dextrin, cellulose, or starch as a dispersed medium of 1 kind or 2 or more kinds. By adding these dispersed mediums, the moisture activity of the enteral effective substances or heat sensitive substances is reduced and the result is that the encapsulated matter's preservability is enhanced. In addition, it is desirable that the addition of the dispersed medium be in the range of 5-50 wt. %. There is no effect on preservability when the amount is less than 5% and when the amount exceeds 50 wt. %, the shape of the capsule is undesirably changed.

The kind of the hardened oil and fat may be oil and fat which does not melt at body temperature (approximately 38°C), and in soybean hardened oil, hardened rape oil, hardened coconut oil or palm kernel oil, and these are used to make adjustments to an appropriate melting point through hydrogen additives. Because hardened beef fat has a melting point of 53°C, it can be used unaltered. It is desirable that the melting point of the hardened oil be in the range of 40-60°C. When less than 40°C, the flowability at room temperature is reduced, and when greater than 60°C, the effect of heat on the encapsulated matter is undesirable.

Granules of enteral effective substances or heat sensitive substances for this invention's entero-soluble capsules are diffused in hardened oil and fat which does not melt at body temperature and are hardened unaltered as capsules only by spraying using a simple nozzle in cooled air.

Consequently, no dissolution occurs at body temperature after orally ingesting these capsules and in addition, the capsules reach the intestine without being decomposed by the stomach or enzymes within the stomach. The hardened oil and fat start to dissolve in the intestine through lipase action within the gastric fluid and the granular enteral effective substances or the heat sensitive substances are exposed within the intestine.

This invention and its effects are explained below through the use of embodiments.

Embodiments

Embodiment 1

Disperse dried strain 450g which contains 5 x 10^{11} units of bifidobacteria per 1g in hardened beef fat (m.p. 53°C) 550g, preserved at 60°C, and while stirring supply to a high pressure pump using a nozzle. Spray the previously described bifidobacteria dispersed liquid from a mono nozzle at an atmosphere temperature of 5°C within a chamber to obtain a capsules whose particle diameters are in the range of 40-600μm.

The amount of bifidobacteria is 3.5 x 10^{10}/g. This capsule, after 3 hours in artificial gastric fluid (pH

3.0) at 37°C, has 3.5 x 10^{10} units/g and even after 3 hours, has a viable cell count of 3.5 x 10^{10} units/g.

Embodiment 2

Using in the core substance the liquid that dispersed in salad oil 30w/w% viable cells of Bifidobacterium longum, perform spray cooling by a mono nozzle using rapeseed hardened oil with a melting point of 53°C as the membrane wall's substance. The core substance is then encapsulated. The average particle diameter of the obtained micro capsule was 200μm.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Embodiment 3

Using in the core substance fluid which had dispersed viable cells of Bifidobacterium longum at a concentration of 10w/w% in hardened oil of melting point 37°C held at a temperature of 40°C and performing spray cooling using a two fluid nozzle, the core material was encapsulated. The average particle diameter of the obtained micro capsules was 100μm, and the viable cell count was 5 x 10^{10} units/g.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Embodiment 4

Using in the core substance fluid which had dispersed viable cells of Bifidobacterium longum at a concentration of 10w/w% in salad oil and using hardened palm oil with a melting point of 58°C as the wall membrane substance, drip into organic liquid (8% ethanol

aqueous solution), cooled to 20°C from a 2 fluid nozzle. The average particle diameter of the obtained micro capsules was 1.5mm and the membrane thickness was 400μm.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Embodiment 5

Disperse vitamin C powder 300g into hardened beef fat (m.p. 53°C) 2.7kg, maintained at a temperature of 60°C and spray cool. The obtained micro capsules were multi-dispersed capsules of vitamin C whose particle diameters were stabilized at approximately 500μm.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Embodiment 6

Disperse bifidobacteria dried granules 100g and corn starch 100g into hardened beef fat (m.p. 53°C) 800g that had been raised to 60°C and spray cool using the method of Embodiment 1. The particle diameters of the obtained capsule were approximately 300μm and the capsule cell count was 5×10^{10} units/g.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Embodiment 7

Disperse bifidobacteria dried powder 150g and powdered skim milk into beef fat hardened oil (m. p. 53°C) 750g that was raised to 58°C and spray cool using the method of Embodiment 1. The particle diameter of the obtained capsule was approximately 100-450μm and the viable cell count was 7.2×10^{10}/g.

Desirable results were obtained in the same way as used in Embodiment 1 for acid resistance experiments.

Effect of the Invention

Because the capsule according to this invention is a fine particle-shaped sphere and because there is no foreign body sensation even after adding other food products with ② acid resistant properties, also after adding to acidic foods or yogurt, no changes occurs due to the acid within the stomach and ③ there is an effective working within the intestine, after reaching and initially beginning to reach the intestine.

Furthermore, ④ compared to conventional encapsulating methods, this invention is a much simpler process and the structure also of the capsule itself is simple. Furthermore, the invention produces the same results as that of conventional capsules.

CLAIMS

1. An entero-soluble capsule dispersing granules comprised of enteral effective substances or heat sensitive substances to hardened oils and fats having melting points exceeding body temperature.

2. The entero-soluble capsule according to Claim 1 wherein the dispersed granules of enteral effective substances or heat sensitive substances is dried lactic acid bacterium comprising as dispersion 1 kind or 2 or more kinds of groups comprised of powdered skim milk, dextrin, cellulose and starch.

3. The entero-soluble capsule according to Claim 1 wherein the enteral effective substances or heat sensitive substances are medicinal substances that are absorbed by the intestinal wall.

4. The entero-soluble capsule according to Claim 1 wherein the melting point of the hardened oils and fats is in the range of 37-60°C.

5. The entero-soluble capsule according to any one of the Claims 1-4 wherein the diameter of the entero-soluble capsule is in the range of 30-1000μm.

Applicant: Snow Brand Milk Products Co., Ltd.
Representative Patent Attorney Funahashi, Eiko

Amendments

23 August 1990

To: Patent Office Examiner Uematsu, Satoshi

1. Disclosure of Matter 1990 Patent Application 193081
2. Title of the Invention

Entero-soluble Capsule

3. Person requesting Amendment

Relationship to Matter Patent Applicant

Snow Brand Milk Products Co., Ltd. 6-1-1-Naebocho, Higashiku, Sapporo, Hokkaido

Representative Shouno, Katsuyo

4. Representative

Location 1-10-1 Nishi Shinbashi Minato-ku Tokyo Shoujikisatsu Building 6th floor Tel. (504) 0717 (telephone number)
Name (8371) Patent Attorney Funahashi, Eiko

5. Subject of Amendment

Column of claims of the specification

6. Details of amendment

Follows separate sheet

[Separate Sheet]

CLAIMS

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3. The entero-soluble capsule according to Claim 1 wherein the enteral effective substances or heat sensitive substances are medicinal substances that are absorbed or not absorbed by the intestinal wall, useful bacteria within the intestine, vitamins or enzymes.

4. The entero-soluble capsule according to Claim 1 wherein the melting point of the hardened oils and fats is in the range of 37-60°C.

5. The entero-soluble capsule according to any one of the Claims 1-4 wherein the diameter of the entero-soluble capsule is in the range of 30-1000μm.